

Doc Code: AP.PRE.REQ

PTO/SB/33 (07-09)

Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)

96700/905

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as ~~first class~~ **Express** mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on May 14, 2010

Signature

Typed or printed name Alan D. Miller

Application Number

10/501,628

Filed

November 22, 2004

First Named Inventor

Alberto Martin

Art Unit

1633

Examiner

Michael D. Burkhart

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).

Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

☒ attorney or agent of record. 42,889
Registration number

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34

Signature

Alan D. Miller

Typed or printed name

212 336 8000

Telephone number

May 14, 2010

Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 35 U.S.C. 132. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.



Dkt. No. 96700/905

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

For : Mutations Caused by Activation-Induced Cytidine Deaminase
Application No. : 10/501,628
Applicants : Alberto Martin and Matthew D. Scharff
Filed : November 22, 2004
Art Unit : 1633
Examiner : Michael D. Burkhardt
Customer No. : 1912
Confirmation No. : 2223

"Express Mail" mailing label No. EL 996374315 US
Date of Deposit: May 14, 2010
I hereby certify that this paper or fee is being deposited
with the United States Postal Service "Express Mail"
service under 37 CFR 1.10 on the date indicated above and
is addressed to the Commissioner for Patents, P.O. Box
1450, Alexandria, VA 22313-1450.
Name: Alan D. Miller
Signature: [Signature]

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents, P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

A Final Office Action was issued on December 30, 2009 in connection with the subject application. A Notice of Appeal and Petition for a Two Month Extension of Time are being filed concurrently with this Request. Accordingly, this Request for Review is being timely filed.

Grounds of Rejection to be Reviewed

Claims 1-9, 13, 15, 18-25, 58, 97, 125 and 262-307 are pending and the subject of this appeal. Claims 1-4, 6-9, 13, 15, 19-22, 24-25, 58, 97, 125, 262-272, 276-284, and 287-307 are rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of the combination of U.S. Patent 5,885,827 ("Wabl") and Muramatsu et al., *Cell* 102: 553-563, 2000 ("Muramatsu"), as evidenced by Martin et al., *Proc. Natl. Acad. Sci.* 99: 12304-8, 2002 ("Martin"). Claims 5 and 23 are rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of the combination of Wabl, in view of Muramatsu, as evidenced by Martin, and U.S. Patent Application Publication No. 2003/0119190 ("Wang"). Claims 273, 274, and 275 are rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of the combination of Wabl, Muramatsu, as evidenced by Martin, and U.S. Patent 5,885,793 ("Griffiths"). Claims 18, 285, and 286 are rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of the combination of Wabl, Muramatsu, as evidenced by Martin, and U.S. Patent 6,815,194 ("Honjo").

Summary of Claimed Subject Matter

The appealed claims are directed to a method of inducing and identifying a mutation in a DNA sequence (e.g., a DNA sequence encoding an antibody), which comprises expressing a

Applicants: Alberto Martin and Matthew D. Scharff

Appl. No.: 10/501,628, page 2 of 5

transgenic activation induced cytidine deaminase (AID) gene in a eukaryotic cell (see the specification at, for example, paragraphs 0101, 0171, 0194, and 0217). The appealed claims also are directed to a method of altering an affinity or specificity of a monoclonal antibody to a first antigen, or altering a cross reactivity of the monoclonal antibody to a second antigen (see the specification at, for example, paragraphs 0096, 0097, 0101, 0171, 0194, and 0217).

Reasons for Withdrawal of Rejection

The Office has failed to establish a *prima facie* case of obviousness because (1) the Office has not provided a credible reason for one of ordinary skill in the art to combine, and then follow, the teachings of the cited references, (2) the Office has not considered the cited prior art as a whole, and (3) the Office has not accorded appropriate weight to the Rule 132 declarations of record.

1. The Office has not Provided a Credible Reason to Combine the Cited References

Applicants maintain that one of ordinary skill in the art would not have chosen AID for the purposes of inducing mutations via deamination of DNA, as required by the appealed claims. As the Supreme Court recently stated, “*there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.*” *KSR Int’l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 U.S.P.Q.2d 1385, 1396 (2007) (emphasis added)). With respect to the present application, the Office has failed to articulate any reasoning with a rational underpinning to support the obviousness rejection in view of the Wabl patent and the Muramatsu reference. In this regard, the Wabl patent discloses a method of performing random mutagenesis of a heterologous target gene using the immunoglobulin hypermutation system. The method involves transfecting an immunoglobulin-mutator-positive cell with a hypermutation-competent expression vector into which has been cloned a target gene, and allowing the target gene to hypermutate. The Wabl patent defines a “mutator positive cell line” as a cell line containing cellular factors that work in combination with enhancers to induce hypermutation.

The Muramatsu reference discloses that overexpression of AID in a lymphoma cell line augments antibody class switching from IgM to IgA without cytokine stimulation. The Muramatsu reference also discloses the generation of AID-deficient mice. AID deficiency completely blocked class switch recombination (CSR) in B cells activated by lipopolysaccharide

Applicants: Alberto Martin and Matthew D. Scharff

Appl. No.: 10/501,628, page 3 of 5

(LPS) *in vitro* and by antigens *in vivo*. In addition, the Muramatsu reference demonstrates that B cells isolated from AID-deficient mice are defective in somatic hypermutation. Based on these results, the Muramatsu reference proposes that AID is an RNA editing enzyme that requires a co-factor for its activity (Muramatsu reference at page 560, first column, and page 561, first column). The candidate co-factors proposed by the Muramatsu reference (Muramatsu reference at page 561, first column) further illustrate that the authors of this publication did not view the deamination activity of AID as responsible for hypermutation, rather, such hypermutation occurred through other enzymatic activities, such as DNA repair enzymes, DNases, and/or DNA polymerases.

Neither the Wabl patent nor the Muramatsu reference discloses or suggests that AID causes mutations by deaminating DNA, as required by the appealed claims. Indeed, the precise mechanism of action of AID was unknown in the art at the time the priority application was filed, as evidenced by the Rule 132 declarations of Michael S. Neuberger, Ph.D., and Matthew D. Scharff, M.D. filed on November 17, 2009. Contrary to the allegations of the Office, at the relevant time AID was one of *many* factors suspected to be involved in somatic hypermutation and CSR, and it was not known or suggested that AID alone is sufficient to directly induce the DNA mutations required for somatic hypermutation (see also, e.g., Delker et al., *Nature Immunology*, 10(11): 1147-1153 (2009), of record).

The Office contends that one of ordinary skill in the art would have followed the combined disclosures of the Wabl patent and the Muramatsu reference and utilized AID to induce mutations via deamination of DNA. For the foregoing reasons, however, one of ordinary skill in the art would not have had a credible reason to do so.

Furthermore, none of the secondary references compensates for the deficiencies of the Wabl patent and the Muramatsu reference. In this respect, the Wang application, the Griffiths patent, and the Honjo patent do not disclose or suggest expressing a transgenic AID gene in a eukaryotic cell and expressing a DNA sequence in the cell, wherein AID initiates mutagenesis by deaminating the DNA sequence. Therefore, the Wang application, the Griffiths patent, and the Honjo patent fail to provide a credible reason for one of ordinary skill in the art to combine the disclosures of the Wabl patent and the Muramatsu reference in the manner set forth by the Office.

2. *The Office has not Considered the Prior Art as a Whole*

As further evidence of the unobviousness of the present invention, the conclusions drawn by the Muramatsu reference with respect to the potential role of AID in SHM are based solely on the phenotype of AID knock-out mice. In this regard, while the Muramatsu reference describes experiments in which AID is overexpressed in mouse B cells, it reports only on the effects of AID overexpression on CSR and not SHM. Appellants have demonstrated that, at the time the application was filed, there were numerous examples of situations in which the phenotype of a gene knock-out (e.g., in a mouse) was difficult to interpret, and even contradicts the phenotype observed when the same gene is overexpressed in a cell or organism.

In considering whether an invention would have been obvious in view of the prior art, the prior art as a whole must be considered, including any prior references that teach away from the invention. Here, the non-obviousness of the appealed claims is particularly evident when proper consideration is given to Gingrich et al., *Curr. Opin. Neurobiology*, 10: 146-152 (2000), and Liu et al., *P.S.E.B.M.*, 223: 344-351 (2000) (both of record), which demonstrate the difficulty associated with interpreting the phenotypes of knock-out mice and transgenic mice.

The Office contends that the Muramatsu reference provides “extensive teachings,” other than knock-out mice, to demonstrate the role of AID in CSR and SHM, and that the references relied upon by Appellants to demonstrate the unpredictability of using gene knockouts relate to “unrelated” genes and are “hardly probative” given the teachings of the Muramatsu reference (see Office Action dated December 30, 2009, at page 7, first complete paragraph). While applicants respectfully disagree with the Office regarding the extensiveness of Muramatsu’s teachings, particularly because the Muramatsu reference does not include data demonstrating that expression of AID actually induces SHM, this does not change the fact that the prior art as a whole demonstrates the unpredictability associated with interpreting phenotypes of knockout and transgenic mice at the time of the present invention.

Therefore, Appellants maintain that one of ordinary skill in the art could not accurately predict the function of a particular protein based solely on the phenotype produced when the gene encoding the protein is disrupted or deleted. For this reason, even if, for the sake of argument, one of ordinary skill in the art were to combine the disclosures of the Wabl patent and the

Applicants: Alberto Martin and Matthew D. Scharff

Appl. No.: 10/501,628, page 5 of 5

Muramatsu reference, the skilled artisan would not arrive at the subject matter of the appealed claims with a reasonable expectation of success.

3. *The Office has not Accorded Appropriate Weight to the Declarations Under 37 C.F.R. § 1.132 of Record*

As discussed herein, the Rule 132 declarations of Michael S. Neuberger, Ph.D., and Matthew D. Scharff, M.D. filed on November 17, 2009, demonstrate, *inter alia*, that the precise mechanism of action of AID was unknown in the art at the time the priority application was filed. In the Office Action dated December 30, 2009, the Office appears to disregard the Rule 132 declarations because of the relationship of Drs. Neuberger and Scharff to the licensee of the present invention. However, the fact that Drs. Neuberger and Scharff are members of the Scientific Advisory Board, and shareholders, of AnaptysBio, Inc., which is a licensee of the present application, does not diminish their well-established positions as experts in the art or the credibility of the statements made in the declarations. Indeed, the Office has not provided any reason why the statements in the Rule 132 declarations are incorrect or inapplicable to the obviousness rejections.

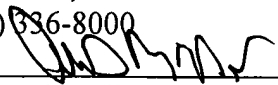
Therefore, particularly in view of Graham factors (see *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966)), it is clear that the present invention would not have been obvious to one of ordinary skill in the art at the relevant time in view of the combination of cited references. Accordingly, Appellants submit that the obviousness rejections under Section 103 are improper.

Respectfully submitted,

AMSTER, ROTHSTEIN & EBENSTEIN LLP
Attorneys for Applicant
90 Park Avenue
New York, New York 10016
(212) 636-8000

Dated: May 14, 2010
New York, New York

By


Alan D. Miller, Reg. No. 42,889